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EXAMINER	
TUCKER, ZACHARY C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,279	MARTIN, THOMAS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9Sep02,7Jan03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

Claims 1-10 have been amended as requested in the correspondence dated 5 February 2004, which is in reply to the Office action mailed 19 November 2003.

Election/Restrictions

The correction of the structure of the elected species, in the correspondence dated 5 Februrary 2004, is noted.

Status of Misjoinder of Invention

In the previous Office action, dated 19 November 2003, claims 1-4 and 6-8 were rejected for misjoinder of invention.

This ground for rejection has been overcome by the amendment to instant claim 1, which limits all compounds according to that claim to one common core; the misjoinder of invention rejection is hereby withdrawn. Claim 1 has now been completely searched.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Wands factors provide a guide for determining whether or not the enablement requirement under 35 U.S.C. 112, first paragraph, has been met:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Claim 10 is drawn to a method of treating an airway disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, hydrate or solvate thereof.

The recitation "an airway disorder" includes all airway disorders. It would not be possible to enumerate here all disorders contemplated by this language. The group, in total, of all airway disorders, only have in common one thing – they affect airways, which includes throat, nose, bronchi, lungs and mouth. Cancers, anatomical deformities, myriad bacterial and viral infections, neurological diseases and exposure to toxins, among others, can cause airway disorders.

(B) The invention according to instant claim 10 is medical.

(C), (D) As evidence of the state of the art with respect to instant claim 10, the following reference is presented:

Burgess, "Mast Cell Tryptase as a Target for Drug Design" Drug News Perspectives, vol. 13(3), pages 147-157 (April 2000).

Chemical compounds having the property of inhibiting the enzymes known as tryptases, as the instantly claimed compounds allegedly posses, were known at the time the invention was made. The prior art acknowledges that such agents hold promise in development of treatments for certain diseases.

Burgess summarizes the state of the art at the time the invention was made, and exemplifies the extent of the knowledge held by one of ordinary skill in the art, in this case, a medical doctor specializing in treatment of airway disorders, about tryptase inhibitors and their application in medicine.

The conclusion reached by Burgess, after a discussion of the current state of the art is simple – that tryptase inhibitors hold promise as therapeutic agents, but no methodology of treating any disease with a tryptase inhibitor had heretofore been developed (page 155). It is not known whether inhibition of tryptase would have an effect on the course of any particular disease, only that elevated levels of mast cells and/or released tryptase is associated with several human diseases like asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic rhinitis, unstable angina, atherosclerosis, psoriasis and multiple sclerosis (page 148).

(E) Burgess addresses the level of predictability with respect to the activity of tryptase inhibitors on page 148. If a compound demonstrates *in vitro* activity as a tryptase inhibitor, this is not predictive of the overall effect that such a compound would have on any particular disease in an animal, and also that activity in one animal does not predict activity in another animal, due to the "profound differences in substrate

specificity, tissue distribution, stabilization requirements and regulatory mechanisms for mast cell tryptases across these various species (including human)..."

(F) Page 46 of the instant specification describes ways in which the active compounds of the invention can be administered in the treatment of respiratory disorders. Inhalation of a micronized powder is taught as the preferred mode of administering compounds of the invention in the treatment of respiratory disorders. Though page 46 teaches a dosage ranging from 0.1-10mg/Kg per day if the active compound is administered *p.o.* or IV, no dosage range is provided for administering compounds of the invention by inhalation.

(G) *In vitro* IC_{50}'s ~~are~~ reported on page 48 of the instant specification for 15 of the compounds according to the invention are the extent of the working examples.

(H) A medical doctor specializing in the treatment of airway disorders would not be capable of developing a method of treatment commensurate in scope with the method according to instant claim 10, given his level of skill and the guidance provided in the instant specification.

Certain of the disorders embraced by the term, "airway disorder" bear no relation to the tryptase enzyme, such as physical deformities, cancers and emphysema associated with tobacco use, and exposure to injurious chemicals. Even those disorders that have been *associated* with abnormalities in tryptase expression are not currently known to be treatable by inhibition of tryptase alone.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, for failing to point out and distinctly claim the subject matter which applicant regards as his invention.

In instant claim 1, Y1 and Y2 are defined as "identical or different and are a 4-11C-heteroaryl or 2-7C-heterocycloalkyl radical containing at least one ring nitrogen..."

Also in claim 1, Z1 and Z2 include as limitations the following moieties: "5-12C-heteroarylene... 3-8C-heterocycloalkylene..."

"Heteroaryl," "heterocycloalkyl," "heteroarylene" and "heterocycloalkylene" are indefinite.

With respect to the recitation of these terms in instant claim 1, this indefiniteness is two-fold. First, the size of the rings is undefined. Only the number of carbon atoms is given. Because the rings do not comprise only carbon atoms (that much is sure), the size of the rings has not been defined – only an open-ended range has been provided limiting the number of nitrogen atoms in the ring to "at least one."

Second, more than one definition of the general term "heterocyclic" or "heterocycle" (and therefore, the variations of these words recited in instant claim 1) is accepted by those of ordinary skill in the art of organic chemistry.

Some consider cyclic organic compounds wherein at least one carbon atom is replaced by sulfur, oxygen or nitrogen to be heterocyclic compounds, while others of ordinary skill include selenium, tellurium, boron or tin containing rings to be within the scope of the term "heterocyclic" as it is commonly used, and some definitions of "heterocyclic" do not require carbon to present at all.

The examiner directs applicants' attention to the following three references:

On page 200 of the McGraw-Hill Dictionary of Chemical Terms, the definition of "heterocyclic compound" is a compound in which the ring structure is a combination of more than one kind of atom.

On page 490 of the Concise Encyclopedia Chemistry, the definition of "heterocycles" is cyclic hydrocarbon compounds in which the ring consists of carbon and at least one other element, usually, N, O or S. The definition goes on to explain that the possibilities for synthesis are nearly unlimited, and that compounds wherein the heteroatoms are of elements like phosphorous, arsenic, selenium, and tellurium are being incorporated with increasing frequency.

On page 594 of Hawley's Condensed Chemical Dictionary, "heterocyclic" is defined as a closed-ring structure, usually, either 5 or 6 members, in which one or more of the atoms in the ring is an element other than carbon, *e.g.* sulfur, nitrogen, *etc.*

These three definitions should make it abundantly clear that there is not one specific and exact definition of the word "heterocyclic," (or the variations thereof presented in the claim at issue here) thus, when this term is present as a claim limitation, the metes and bounds of protection are not pointed out and distinctly claimed. Though the three above-cited definitions of the term have some shared aspects, chemists of ordinary skill would not necessarily agree on the full scope and meaning of the terms.

Applicants may argue that the objected-to terminology has been fully defined in the specification, and therefore the requirements of 35 U.S.C. 112, second paragraph, have been met with respect to claim 1.

The examiner would respond by pointing out the fact that while it is proper to use the specification to interpret what the applicant meant by a word or phrase recited in the claim, it is **not** proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen;* 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994); *Intervet America Inc. v. Kee-Vet Lab. Inc.,* 887 F.2d 1050, 1053, 12 USPQ2d 1474, 1476 (Fed. Cir. 1989).

Claim 1 is also indefinite because, though the claim requires 20 to 40 bonds to be present between "the terminal nitrogen" atoms in the compound of formula I, a compound according to formula I need not have any terminal nitrogen atoms, or may only posses one terminal nitrogen atom. The groups K1 and K2 in the formula I are defined in the alternative as terminating in a group Y1 or Y2, respectively. Y1 and Y2 are heterocyclic, and though not distinct and concrete as pointed out above, those of ordinary skill in the art would at the least agree on the point that a heterocyclic ring as recited in Y1 and Y2 need not posses a nitrogen atom substitution attached thereto. Thus, the recitation in instant claim 1 of "where on the direct route between the terminal nitrogen atoms 20 to 40 bonds have to be present," is indefinite because the compounds need not posses any terminal nitrogen atom at all.

The requirement of there having to be 20 to 40 bonds present between the terminal nitrogen atoms is further indefinite because it is unclear which nitrogen atoms are to be considered terminal, since the variables X1 and X2 include eight different

functional groups which terminate in more than one nitrogen atom. It is unclear which of the nitrogen atoms in these particular functional groups is to be considered the "terminal nitrogen atom(s)." A logical problem arises also from the fact that *within* the multi-nitrogen-atom-terminated groups X1 and X2, there are two terminal nitrogen atoms. It would not be possible for 20 to 40 bonds to be present between these nitrogen atoms (which are terminal) that are separated by only a few other atoms, yet this particular configuration is in fact claimed.

Claims 2-10, since all depend from an indefinite claim, are also indefinite and therefore rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Rødbotten et al, "Stereoselective Synthesis of Alkynylglycines and α,α'-Alkynyl-Bridged Bis(glycines)" Acta Chemica Scandinavica, vol. 51, pages 873-880, (1997).

MPEP 2173.06 directs the examiner to apply art against a claim rejected under 35 U.S.C. 112, second paragraph, if one interpretation of such a claim would render it unpatentable over the prior art.

Rødbotten et al discloses a compound according to instant claim 1 where, if one counts each and every bond which is present on the direct route *between* the two terminal nitrogen atoms in that compound, no less than 28 bonds *are present*. This is the compound designated **12** on page 876 of Rødbotten et al. The most direct route between the two nitrogen atoms in Rødbotten et al's compound **12** is a straight line drawn from one nitrogen atom to the other. Along the length of such a line between the two nitrogen atoms, 28 covalent bonds are present in that molecule.

All of the bonds present on the direct route between the terminal nitrogen atoms in compound **12** includes all of the C-H bonds, the C-O bonds in the carboxylate group and the O-H bond in the carboxlate group. The only bonds not present on the direct route between nitrogen atoms are the N-H bonds, which are not counted. Double bonds and triple bonds are counted as one bond.

Rødbotten et al's compound **12** is a compound according to instant claims 1 and 2 wherein B1, B2, A1 and A2 are bonds, B3 and B4 are C1 alkylene (substituted with –COOH), A3, A4, B5, B6, A5 and A6 are bonds, and K1 and K2 are $-NH_2$.

Pages 6 and 7 of the instant specification illustrate the determination of the number of bonds on the direct route between two terminal nitrogen atoms. As pointed out above in the rejections under 35 U.S.C. 112, second paragraph, limitations from the specification cannot be read as claim limitations. Even if doing so were proper in this case, the illustration on pages 6 and 7 of the specification does not pertain to counting the number of bonds *present between* the two nitrogen atoms on the direct route, so it is not consonant with the language recited in instant claim 1 and thus does not limit claim

1 insofar as the limitation on the number of bonds which have to be present between these atoms. The first line of page 7 is noteworthy – "Here, the direct route comprises 33 bonds." As applicants are aware, "comprising" is open language that does not limit the number of bonds on that direct route to only 33, which is not inconsistent with the examiner's interpretation of claim 1.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Crisp et al, "Elaboration of the Side-Chain of Amino Acid Derivatives by Palladium Catalysed Couplings" Tetrahedron, vol. 53(51), pages 17489-17500 (1997).

MPEP 2173.06 directs the examiner to apply art against a claim rejected under 35 U.S.C. 112, second paragraph, if one interpretation of such a claim would render it unpatentable over the prior art.

Crisp et al, on page 17491, discloses a compound designated **2**, which is a compound according to instant claims 1 and 2 where B1, B2, A1 and A2 are bonds, B3 and B4 are C1 alkylene (substituted with $NHCOCH_3$), A3, A4, B5, B6, A5 and A6 are bonds, and K1 and K2 are $-C(O)NH_2$.

Crisp et al's compound **2** has no less than 33 bonds present on the direct route between terminal nitrogen atoms (in this case, the nitrogen atoms of the NH_2 group are considered the terminal nitrogen atoms, and the bonds were counted as explained in the rejection based on Rødbotten et al).

Allowable Subject Matter

Claims 5 and 8 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

It is suggested that claims 5 and 8 be rewritten in independent form, since they are directed to ultimate species.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday-Friday from 6:30am to 3:00pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-2717.

zt

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624